REMARKS

This Application has been carefully reviewed in light of the Final Office Action mailed November 28, 2006. At the time of the Final Office Action, Claims 1, 3-6, 8-14 and 17 were pending in this Application. Claims 1, 3-6, 8-14 and 17 were rejected. Claims 1, 6 and 11 have been amended to further define various features of Applicants' invention. Claims 12, 13 and 14 have been cancelled without prejudice or disclaimer. Claims 2, 7, 15 and 16 were previously cancelled without prejudice or disclaimer. Applicants respectfully request reconsideration and favorable action in this case.

Summary of telephone interview

Applicants agree with the Examiner's Interview Summary mailed on January 30, 2007 of the telephone interview conducted on January 23, 2007.

Rejections under 35 U.S.C. § 112

Claims 1, 3-6, 8-14 and 17 were rejected by the Examiner under 35 U.S.C. §112, second paragraph, as being indefinite and failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 1, 3-6, 8-14 and 17 were also rejected by the Examiner under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner stated that various recitations of "avoids removal of significant amounts of immunoglobulin and similar large molecules" are vague and indefinite.

The Examiner stated the claims are indefinite and the scope and range of terminology "significant amounts" and "similar large molecules" are unclear.

The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention.

The Examiner stated there is no clear concise support for the recitation of "avoids removal of significant amounts . . ." or "similar large molecules" in the instant Specification and such recitations constitute new matter.

Applicants respectfully submit that the phrase ". . . during the very large pore hemofiltration which avoids removal of significant amounts of immunoglobulins and similar large molecules . . ." as used in previously presented Claims 1, 6 and 11 is well defined in the Specification. The phrase ". . . selected to avoid removal of significant amounts of immunoglobulins and similar large molecules . . ." as used in previously presented Claim 17 is also well defined by the specification. These phrases also clearly distinguish Applicants' invention from various references cited by the Examiner.

Such claim terminology satisfies all requirements of 35 U.S.C. § 112 and is well defined in the Specification. Applicants have highlighted various portions of the following quotes from the Specification which relate to defining terms "significant amounts" and "similar large molecules." For example the Specification states:

> . . . a new type of hemofiltration referred to as very large pore hemofiltration ("VLPH") is provided. Very large pore hemofiltration includes sustained removal of albumin and similar large receptor molecules and carrier molecules for the purpose of removing both bound and unbound pathologic molecules or toxins.

Specification page 8, lines 3-9.

> Therefore, a very large pore hemofiltration membrane suitable for the therapy of the present invention often requires a nominal molecular weight cutoff of >100 kD. Hemofilters with a nominal molecular weight cutoff ≤100 kiloDalton are generally not capable of sustained effective removal of albumin, and large receptor and carrier molecules, especially when target molecules are bound to them.
>
> VLPH is distinct from plasmapheresis in the following critical ways. First, VLPH seeks sieving of proteins such as albumin, soluble tumor necrosis factor receptor 75 (molecular weight =

> 75,000 Dalton), and similar soluble receptor and carrier molecules for the reasons stated above. VLPH specifically avoids removal of significant amounts of immunoglobulins and similar large molecules because removal of these molecules is associated with a marked increase in the risk of opportunistic infection.

Specification page 8, line 26-page 9, line 12.

> Examples of Very Large Pore Hemofiltration and Plasma Colloid Exchange Therapy.
>
> For use in IMRD, liver failure, exogenous intoxications and other conditions associated with toxins in the blood, the present invention teaches a very large pore hemofilter with a membrane capable of sieving a significant amount of target molecules, target receptor molecules, and target complex molecules over a significant portion of the therapy time. The very large pore hemofilter will typically have a sieving capacity sufficient to provide for an appropriately rapid exchange of target complex molecules that are circulating in plasma, and removing target molecules located in tissues.

Specification page 18, lines 10-22.

> A sieving coefficient approaching (or even exceeding) 1.0 for target complex molecules (or other target molecules) may often provide the most efficient removal of target molecules, and in certain circumstances will be most desirable. Sieving coefficients for target complex molecules (and target molecules) above 0.5 will also be reasonably effective. Lower sieving coefficients (between about 0.05 and 0.5) may provide

> sufficiently effective sieving under certain treatment circumstances. Sieving coefficients that are too low either initially or after membrane polarization are considered inadequate for VLPH.
>
> The sieving characteristics of membrane pores depends not only on the nominal pore size, but also on the physical, chemical, and electrical characteristics of the material from which it is made and the particular manufacturing technique used to produce the membrane. As a result, the sieving coefficient for albumin and other target receptor molecules, and target molecules, may vary among membranes with the same nominal pore size. However, the nominal molecular weight cutoff to provide adequate sieving of target receptor molecules, target complex molecules, and target molecules, is expected to be approximately 150,000 to 500,000 Dalton. Very large pore hemofilter 102 will typically have pores with a molecular weight cutoff substantially less than that of plasmapheresis filters, so that no significant amount of immunoglobulins and similar large molecules will be sieved from the blood.
>
> A 150-500 kD very large pore hemofilter may be used to accomplish plasma colloid exchange therapy (PCET) in accordance with teachings of the present invention.

Specification page 21, line 25-page 22, line 25.

The above quotes clearly indicate that Applicants have not added any "new matter" to the amended claims.

To expedite allowance of pending claims, Claim 1, 6, 11 and 17 have been amended by deleting the phrase "similar large molecules".

A person skilled in the art of Applicants' invention as defined in the pending amended claims would understand as a minimum, various types of equipment and procedures used to filter blood when the present Application was filed. The "Atlas of Hemofiltration" published in 2002 is representative of the level of knowledge of a person having reasonable skill in the art at the time Applicants filed the present Application. Applicants have attached copies of the cover page, contents, contributors, preface and pages 1-14 from this document. The information contained on pages 11-14 may be particularly helpful in defining general level of knowledge of a person skilled in the art at the time of Applicants' invention. Applicants will also provide the Examiner with a complete copy of this booklet if requested.

Applicants further note that plasma colloid replacement fluid, plasma colloid replacement fluid kits and extracorporeal blood circuits as defined in the pending claims will be used by highly skilled medical personnel to treat a wide variety of inflammatory mediator related disease (IMRD), liver failure, exogenous toxin exposure and other conditions associated with toxins in the blood. Such treatments may be generally described as plasma colloid exchange therapy (PCET) which are described in more detail in the Specification. The personnel associated with design and manufacture of such equipment will also be highly qualified and highly trained.

> Removal or exchange of target molecules, target receptor molecules, and target complex molecules depends on a number of variables. These variables include duration of therapy, membrane sieving coefficients for target molecules, target receptor molecules, and target complex molecules, and filter blood and ultrafiltrate flow rates, among others. Short duration (but intense) therapy can rapidly remove target molecules, target receptor molecules, and target complex molecules from plasma, but may leave insufficient time for target molecules, target receptor molecules, and target complex molecules to move from tissue sites into plasma, thus limiting the total body reduction of target molecules. Longer treatment times will

> allow for movement of target molecules from tissues, but, if sieving coefficient is excessively high, then plasma colloid replacement fluid would not be efficiently used. Filter blood and ultrafiltrate flow will also materially affect efficiency of treatment. Appropriate treatment duration will depend on the nature of the pathophysiologic condition to be treated, its severity, and other relevant clinical factors as assessed by a physician. Thus, the combinations of treatment duration, sieving coefficient, and filter blood and ultrafiltrate flow will vary.

Specification, Page 21, lines 1-24.

The terminology used in the pending claims would be well understood by personnel skilled in the art of preparing and/or using replacement fluids associated with hemofiltration. The terminology used in the pending claims will be well understood by personnel skilled in the art of designing and/or operating extracorporeal blood circuits and hemofiltration equipment.

Claims 1, 6, 11 and 17 have been amended to clarify various features of Applicants' invention. Applicants request withdrawal of all rejections under 35 U.S.C. § 112 and allowance of the pending claims as amended.

Rejections under 35 U.S.C. § 103

In order to establish a prima facie case of obviousness, the references cited by the Examiner must disclose all claimed limitations. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Furthermore, according to § 2143 of the Manual of Patent Examining Procedure, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest

all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Claims 1, 3-6 and 8-10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,900,720 issued to Ronald Kotitschke ("Kotitschke") in view of U.S. Patent No. 5,919,369 issued to Stephen R. Ash ("Ash"), U.S. Patent No. 5,661,124 issued to Stephen J. Hoffman et al. ("Hoffman") and U.S. Patent No. 4,968,432 issued to Glenn D. Antwiler ("Antwiler"). Applicants respectfully traverse and submit the cited art combinations, even if proper, which Applicants do not concede, does not render the claimed embodiments of the invention obvious.

Applicants note that the Examiner has relied upon combining various portions of four references (Kotitschke, Ash, Hoffman and Antwiler) to reject independent Claims 1 and 6. Applicants note that the Examiner has not cited any basis or support for such combinations other than teachings of Applicants' invention as defined by the pending claims and as more further described in Applicants' specification and drawings. Applicants respectfully submit that without having first reviewed and studied Applicants' specification and amended Claims 1 and 6 there would be no basis for making such combinations. Even if the combinations are made, as the Examiner suggested, the results will not be Applicants' plasma colloid replacement fluid as defined in amended Claims 1 and 6.

Neither Kotitschke, Ash, Hoffman and/or Antwiler show or teach a replacement fluid having clean target receptor molecules as defined in amended Claims 1 and 6.

Kotitschke (See Column 4 lines 50-68 and Column 5, lines 1-5) contemplates more rapid restoration of a protein profile with his fluid. He discloses no function for the fluid, other than more rapid restoration of the protein profile. The named molecules in Kotitschke **are not** well suited for use as Applicants' "target receptor molecules". Applicants' invention as defined in amended Claims 1 and 6 calls for a replacement fluid for a specific function.

Applicants' invention is not related to plasma composition, other than maintenance of colloid pressure with albumin.

Applicants' claimed replacement fluid provides clean target receptor molecules that function in a patient to achieve a specific goal (removal of toxins). Kotitschke fluid is infused and left in a patient. Applicants' claimed replacement fluid with clean target receptor molecules is infused with the specific intention of later removing the same molecules loaded with toxins during the same treatment. Applicants' claimed invention differs completely in composition and purpose as compared to Kotitschke. Very large pore hemofiltration is convective or dialytic removal of target molecules, using an actual ultrafiltrate flow which may be discarded. Hence the need for Applicants' claimed replacement fluid.

Kotitschke teaches a replacement fluid for plasmapheresis. The goal of plasmapheresis is to remove plasma and specifically avoid removal of red cells, white cells and platelets. Kotitschke fluid incorporates no blood cells or hemoglobin.

Kotitschke is clearly directed towards replacement of a patient's plasma with a substitute medium which does not contain blood coagulation factors. Kotitschke teaches a fluid with a protein concentration of about seventy-five grams per liter and does contain most essential serum proteins. Applicants respectfully submit that Kotitschke is directed toward therapeutic plasmapheresis. See column 1, lines 8-21 of Kotitschke.

Kotitschke discloses fluids containing immunoglobulins. See, e.g. Col. 3, lines 38-44. Further it identifies immunoglobulins IgG, IgA and IgM as "the most essential human serum proteins in the plasma-exchange medium." Col. 3, lines 29-33. This need for immunoglobulins is logical because Kotitschke needs to provide a plasmapheresis replacement fluid. By design plasmapheresis removes immunoglobulins. Kotitschke teaches removing immunoglobulins presented to a membrane. In contrast, very large poor hemofiltration may be performed using an effective molecular weigh cutoff that does not remove significant amounts of immunoglobulins. By identifying immunoglobulins as "essential" in its plasma-exchange medium, Kotitschke teaches against using any replacement fluid that does not contain immunoglobulins.

Kotitschke clearly teaches a blood filtration process that removes significant amounts of immunoglobulins and similar large molecules. Kotitschke relates to a sterile plasma-

exchange medium. See Kotitschke, Col. 1, lines 7-8. Such a medium is designed to replace fluid removed during plasmapheresis. See Kotitschke, Col. 1, lines 9-14. As stated in Applicants' Specification ". . . [v]ery large pore hemofilter 102 will typically have pores with a molecular weight cutoff substantially less than that of plasmapheresis filters, so that no significant amount of immunoglobulins and similar large molecules will be sieved from the blood." Specification, p. 23, lines 17-22. Applicants' specification also indicates that the plasma colloid replacement fluid includes "albumin and/or other target receptor molecules and/or other physiologic molecules in a sufficient concentration to adequately replenish ongoing losses." Specification, p. 25, lines 1-5.

The Examiner made specific reference to column 3, lines 45-51 of Kotitschke. Applicants respectfully submit that the remaining portions of Kotitschke column 3 clearly show that Kotitschke serum-protein solutions are substantially different from Applicants' plasma colloid replacement fluid as defined in amended Claims 1 and 6. Kotitschke expressly teaches a replacement fluid which allows reducing the amount of albumin included within the replacement fluid. For example, Kotitschke states "the organism responds to a plasma exchange with the 5.0% serum-protein solution just as it does, though in a diminished form, to an exchange involving the 5.0% albumin solution . . . ." See Kotitschke column 3, lines 65-68. Claim 1 of Kotitschke teaches replacement of a patient's plasma with a substitute medium having 35 to 50 grams per liter of albumin and along with immunoglobulins and other serum proteins.

Applicants' replacement fluid as defined in amended Claims 1 and 6 is not directed towards leaving the plasma-protein profile of the patients treated practically unchanged. One of the objects of Kotitschke is to provide a medium for therapeutic plasma exchange which results in the plasma-protein profile of treated patients being practically unchanged. See Kotitschke column 3, lines 19-24. Specific concentrations, percentages, volumes and/or fluid flow rates will naturally vary as required to treat each patient. See Specification, p.21, lines 1-24.

Applicants' invention as defined in amended Claims 1 and 6 clearly calls for a plasma colloid replacement fluid for replacing target receptor molecules ". . . removed from a patient's blood during very large pore hemofiltration which avoids removal of significant

amounts of immunoglobulins and similar large molecules . . . ." The sterile plasma exchange medium of Kotitschke is clearly directed toward being used with plasmapheresis systems which do remove significant amounts of immunoglobulins and similar large molecules. As stated on column 4, lines 11-21 of Kotitschke "the invention derives from the surprising results of a study involving a seventy-five percent plasma exchange carried over an interval of several months on five healthy volunteers . . . ." Kotitschke clearly does not show or teach a plasma colloid replacement fluid having ". . . a pharmaceutical grade balanced salt solution having clean target receptor molecules corresponding with the contaminated target receptor molecules which have been removed from the patient's bloodstream during the very large pore hemofiltration which avoids removal of significant amounts of immunoglobulins and similar large molecules . . . ." Applicants respectfully submit that Kotitschke clearly teaches away from Applicants' invention as defined in amended Claims 1 and 6.

Hoffman teaches a blood substitute which may be used when it is not practical to transfuse a patient with donated blood. The blood substitute of Hoffman is appropriate for use when substantial amounts of blood have been removed from a patient. The Examiner noted that column 20, line 60 through column 21, line 25 of Hoffman provides one example of this type of blood substitute. Hoffman does not make any reference to blood filtration or replacement fluids while filtering blood. Specifically, Hoffman makes no reference to any procedure such as very large pore hemofiltration as defined in amended Claims 1 and 6. Applicants respectfully submit that the Examiner has not cited any basis to combine Kotitschke and/or Hoffman with any of the other references. Applicants respectfully submit that **Kotitschke and Hoffman expressly teach away from each other** and away from Applicants' invention as defined in amended Claims 1 and 6.

Ash oscillates toxins out of a plasma water, across a membrane, and into a sorbent solution. Ash teaches using sorbents in an extracorporeal blood circuit to adsorb toxins. The sorbents can only have an impact on the plasma that they "see" fluxing back and forth across an extracorporeal membrane.

Applicants' claimed invention infuses clean target receptor molecules into a patient, where the receptor molecules may directly interact with a patient's tissues and total blood

supply. Adsorbing toxins with clean target receptor molecules in a patient's tissues and total blood supply may be dramatically more effective than the Ash extracorporeal method. Applicants' claimed invention is based on the dynamics of removing toxins from within a patient's body.

Ash teaches the use of a filtration process such as hemofiltration or plasma filtration to remove protein-bound and middle molecular weight toxins by circulating a sorbent suspension against exterior surfaces of a fiber membrane. See Ash Col. 2, lines 41-61. Ash describes various types of plasma filtration and/or hemofiltration membranes. In the context of his methods and apparatus for using sorbent suspensions circulating over the exterior of hollow fiber membranes, Ash notes that preferred plasamafiltration or hemofiltration membranes will have pore sizes which transmit albumin or other middle molecular weight molecules with selectivity over larger molecules. See column 7, lines 1-24 of Ash. However, the example provided by Ash "Plasmaflow AP-05H(L) plasma separator" has about 1,000,000 m.w. cuttoff. See Ash column 7 lines 14-16. Ash does not show or teach the use of any replacement fluid having albumin.

Ash expressly teaches ". . . plasma filtration or hemofiltration methods of the invention are advantageously performed in connection with a preferred, dialysis instrument including a parallel plate dialyzer and moving the sorbent suspension formulation in a counter-current mode by the direct application of alternating negative pressure and positive pressure on the dialysate side . . . . The preferred system also creates a slide back and forth motion of the sorbent suspension formulation, which agitates, locally mixes and helps to prevent settling of the suspension." See Ash, Col. 7, lines 55-65.

Ash does not show or teach the use of any replacement fluid having albumin. Ash expressly teaches the use of reinfusate bag 41 and prime bottle 42. See Figure 2 of Ash. Ash expressly teaches "Reinfusate solution (e.g., $CaCl_2$ solution and appropriate amounts of KCl and/or NaCl solution) is injected into reinfusate bag 41. Reinfusate line 26 is connected to reinfusate bag 41 and a drip chamber in the line is partially filled. Prime tube 23 is connected to prime bottle 42 containing priming fluid (e.g., 5% dextrose) if desired replacement fluid can be provided via replacement line 43." See Ash, Col. 9, lines 44-51. Ash does not show or teach any use of fluids such as taught by Kotitschke and/or Hoffman. Applicants

respectfully submit that Ash does not show or teach a replacement fluid for use with very large pore hemofiltration as further defined in amended Claimed 1 and 6.

Applicants note that Antwiler expressly teaches the use of a continuous plasma regeneration system to regenerate plasma separated from a patient's body by a plasma exchange system. See Col. 2, lines 11-15 of Antwiler. Antwiler further teaches removing a constituent of biological fluid including a blood component such as low density lipoproteins (LDL's) and very low density lipoproteins (VLDL's) from a patient's blood.

Antwiler expressly teaches the use of a dialyzer having a semipermeable membrane in combination with a first precipitation agent solution which cooperate with each other to form a plasma flow from the dialyzer. A second precipitating agent is added to the plasma stream which then flows to another dialyzer which includes a semipermeable membrane operable to separate the plasma from a counterflowing dialysate. The regenerative plasma then flows from the second dialyzer into a plasma exchange system for return to the patient. See Antwiler, Col. 2, lines 11-66. Antwiler does not show or teach any replacement fluid for use during very large pore hemofiltration as further defined in amended Claim 1.

Claim 6 has been further amended to call for ". . . the clean target receptor molecules consisting essentially of albumin, receptor molecules and carrier molecules with sufficient clean albumin to maintain adequate plasma oncotic pressure during the very large pore hemofiltration which avoids removal of significant amounts of immunoglobulins." None of the references cited by the Examiner show or teach Applicants' invention as defined in Amended Claim 6. Applicants respectfully request withdrawal of all rejections and allowance of Claims 1 and 6 as amended.

Applicants respectfully traverse the Examiner's comments that Kotitschke teaches a replacement fluid having clean target reception molecules as defined in dependent Claims 5 and 10. Applicants' invention does not remove significant amounts of immunoglobulins. Therefore, Kotitschke's replacement fluid which contains immunoglobulins and macroglobulins does not show or teach Applicants' invention as defined in Claims 5 and 10.

Claims 3, 4 and 5 are dependent from Claim 1. Since Claim 1 as amended is now deemed allowable, Claims 3, 4 and 5 are also allowable. Applicants request withdrawal of all rejections and allowance of Claims 3, 4 and 5.

Claims 8, 9 and 10 are dependent from Claim 6. Since Claim 6 as amended is now deemed reliable, Claims 8, 9 and 10 are also allowable. Applicants request withdrawal of all rejections and allowance of Claims 8, 9 and 10 as previously amended.

Claims 11-14 and 17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Antwiler in view of Ash, Kotitschke and Hoffman. Applicants respectfully traverse and submit the cited art combinations, even if proper, which Applicants do not concede, does not render the claimed embodiments of their invention obvious.

As previously noted Antwiler does not show or teach a plasma colloid replacement fluid kit as further defined in amended Claim 11. Applicants expressly traverse the Examiner's statement that the meaning of "kit" is an assembled set of parts or materials. A more appropriate definition for the word "kit" is a set of articles or parts for a specific purpose. The Specification expressly states " . . . replacement fluid source 150 may be generally described as a replacement fluid kit. Multiple replacement fluid kits may be maintained in the vicinity of hemofilter 102." See Specification page 25 lines 13-16.

Antwiler does not show or teach an extracorporeal blood circuit in combination with a source for infusing a replacement fluid as further defined in Claim 17. Antwiler expressly teaches alternative source 64 of replacement fluid. For example, Antwiler does not show or teach an extracorporeal blood circuit having various features of Applicants' invention including, but not limited to, the blood filter having an effective molecular weight cut-off greater than 150,000 Daltons and ". . . the effective molecular weight cut-off of the blood filter selected to avoid removal of significant amounts of immunoglobulins and similar large molecules" in combination with a replacement fluid as further defined in Claim 17.

Claim 17 has been further amended to call for ". . . the replacement fluid consisting essentially of a pharmaceutical grade balanced salt solution with sufficient clean albumin to maintain adequate plasma oncotic pressure with ultrafiltration rates between approximately

two liters per hour and twenty liters per hour and other target receptor molecules in a sufficient concentration to adequately replenish ongoing losses."

As previously noted Ash, Kotitschke and Hoffman do not show or teach Applicants' replacement. None of these references show or teach an extracorporeal blood circuit in combination with a source for infusing a replacement fluid at ultrafiltration rates as defined in amended Claim 17.

Applicants request withdrawal of all rejections and allowance of Claims 11 and 17 as amended.

CONCLUSION

Applicants have now made an earnest effort to place this case in condition for allowance in light of the amendments and remarks set forth above. Applicants respectfully request reconsideration of the pending Claims as amended.

Applicants believe there are no fees due at this time, however, the Commissioner is hereby authorized to charge any fees necessary or credit any overpayment to Deposit Account No. 50-2148 of Baker Botts L.L.P.

If there are any matters concerning this Application that may be cleared up in a telephone conversation, please contact Applicants' attorney at 512.322.2599.

Respectfully submitted,
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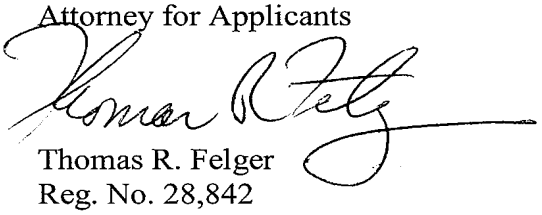

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Enclosure: Copies of cover page, contents, contributors, preface and pages 1-14 from the "Atlas of Hemofiltration" published in 2002